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14. ABSTRACT

In this project, we proposed to develop the imaging method for early detection of amyloid plaque in Alzheimer's disease. As specified in SA#1 and the project timeline, the major tasks of year 1 are the construction and optimization of a prototype x-ray phase contrast CT system to carry out the tasks specified in SA#2 and #3. Thus far, the construction of the prototype x-ray phase contrast CT is progressing well and is in the optimization process as anticipated. The major challenge of building the prototype x-ray phase contrast CT is the fabrication of x-ray gratings at high precision and performance. Enabled by the cutting-edge opti-mechanical equipment and devices at the Nano-Technology Research Center of GaTech (see Fig. 1), we have gained a plenty of experience in fabricating the x-ray gratings through a trial and error optimization process. We have also built three modules that are ready for filling of Aβ-peptide and Aβ-peptide/fibril to make the Aβ-peptide phantoms to carry out the tasks specified in SA#2. Thus far, under partial support of this award, two journal papers have been published in *Medical Physics* – one of the leading journals in medical imaging, and five papers published in leading international conferences. Overall, the project's progression has been in pace with the project timeline specified in statement of work (SOW).

15. SUBJECT TERMS
Alzheimer disease, Amyloid plaque, X-ray phase contrast, X-ray phase contrast imaging, X-ray phase contrast CT

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Introduction

A. Overall: As the elderly population increases, dementia due to Alzheimer's disease (AD) has emerged as a major health threat[1-3]. Recently, the x-ray CT based on a new imaging mechanism – refraction – is emerging to improve CT's capability of differentiating soft tissues[4-10]. Hence, we propose to develop the x-ray phase contrast CT imaging method with an x-ray tube and gratings to directly detect amyloid plaques in Alzheimer's brain without the involvement of contrast agent or molecular probes. The project started on 05/15/2012. Here is the annual report of the project's progress in year 1.

B. Specific Aims:

Three Specific Aims specified in the proposal's Statement of Work (SOW), which are repeated below:

SA#1 Develop and optimize an x-ray phase CT to explore the methodology of direct imaging of AP;
Outcome: An x-ray tube- and grating-based phase CT as the foundation for the pursuit of SA #2 and #3.

SA#2 Evaluate the x-ray phase CT's capability of imaging $A\beta_{1-40}$/$A\beta_{1-42}$ peptides/fibrils at the concentrations existing in AD brain;
Outcome: A quantitative understanding of x-ray phase CT's capability in imaging the $A\beta_{1-40}$ and $A\beta_{1-42}$ fibrils.

SA#3 Verify the x-ray phase CT's capability of direct imaging of AP in AD using postmortem brain specimens.
Outcome: Quantitatively evaluated and verified performance of x-ray phase CT for imaging APs in AD.

C. Project Timeline:

The project timeline specified in the project's SOW is also listed below:

Tasks	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12
D.1.1: System construction												
D.1.2: System optimization												
D.2: Performance: Phantom study												
D.3: Performance: Specimen study												

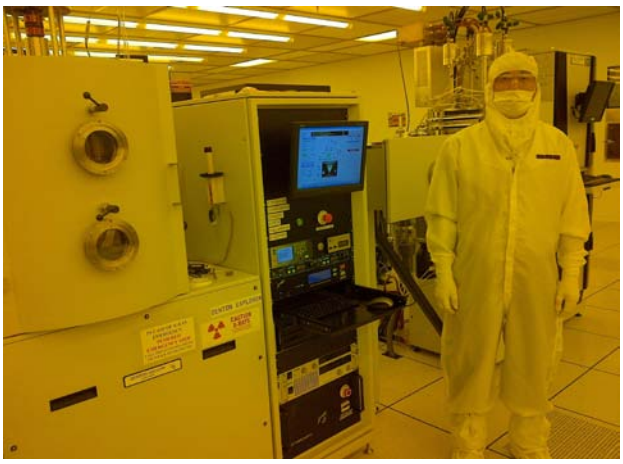

Figure 1. A picture showing that the principal investigator is in the clean room of GaTech's Nano-Technology Research Center, standing by the Denton Explorer E-beam evaporator for the fabrication of grating G2, a key component of x-ray tube and grating-based x-ray phase contrast CT imaging method.

Body

According to the project timeline, the major tasks in the first year are the System Construction and Optimization, in which a micro-focus x-ray tube, a CMOS x-ray detector with 50μm detector cell dimension, and the two key components – x-ray gratings G1 and G2, are to be integrated.

A. **Subsystem/components – Grating G1 and G2**: The fabrication of grating G1 and G2 is very challenging, since the wavelength of x-ray is very short. Using the cutting-edge opto-mechanical and chemical equipment and devices, a set of two x-ray gratings (G1 and G2) for SA#1 are being fabricated at the GaTech's Nano-Technology Research Center (NTRC) (see Fig. 1). Thus far, the progress in the fabrication of G1 is better than that of G2, but their opto-mechanical properties, especially those of G2, are not satisfactory yet. Intensive effort is being devoted to optimizing the fabrication recipes and processes of gratings G1 and G2 to reach the satisfactory performance.

Shown in Fig. 2 (a) is a picture with grating G1 installed. The period of G1 is approximately 4 μm, and thus its micro-structure is not visible to naked eyes. Presented in Fig. 1 (b) is a picture to show the micro-structure of G1, which was taken by a microscopic camera at 50 times magnification. Once the gratings G1 and G2 with satisfactory performance are obtained, their three-dimensional micro-structures will be demonstrated with pictures taken by SEM (scanning electron microscope).

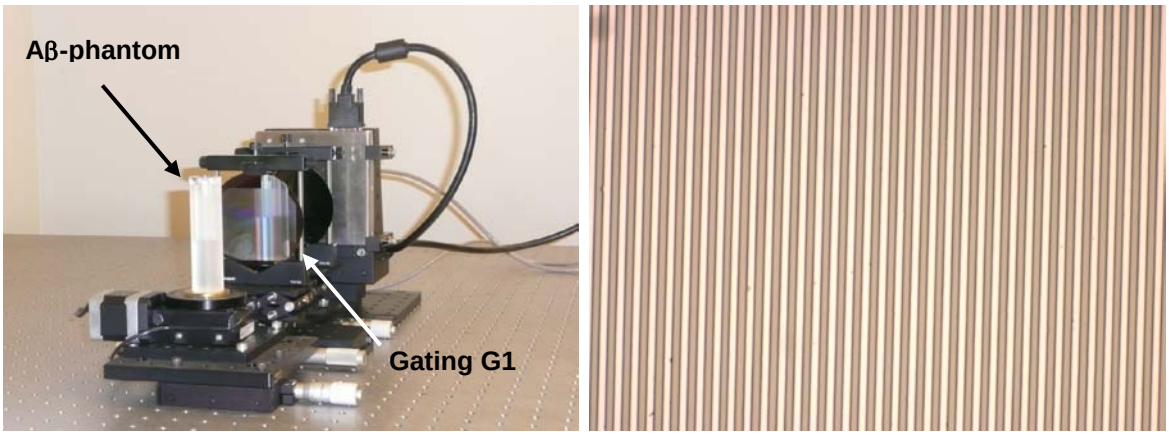

Figure 2. A picture showing the gratings and phantom installed in the prototype x-ray phase CT system (a) and the micro structure of grating G1 taken by microscopic camera at 50 time magnification (b).

B. **Subsystem/components – Aβ-peptide phantoms**: As specified in SA#2 of the SOW, using the specially designed Aβ-phantoms, we'll investigate the contrast-to-noise ratio (CNR) of $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ fibrils in the x-ray phase contrast CT imaging, as a function over the molar concentrations corresponding to normal, pathologic and Alzheimer's brains, in which the amyloid precursor protein (APP) will be included as a reference. Toward this goal, we have made three PMMA (Polymethyl methacrylate) frames for the fabrication of the Aβ-phantoms, and shown in Fig. 3 are the major parts (bodies and caps). As specified in the proposal, the tunnels drilled in the PMMA body will be filled with $A\beta_{1\text{-}40}$/$A\beta_{1\text{-}42}$ peptides/fibrils solutions at selected concentrations (see Table I). The Aβ-phantoms with the $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$ fibrils filled and sealed will be installed in the rotation stage of the prototype x-ray phase contrast CT in the way illustrated in Fig. 2 (a) to carry out the tasks toward SA#2.

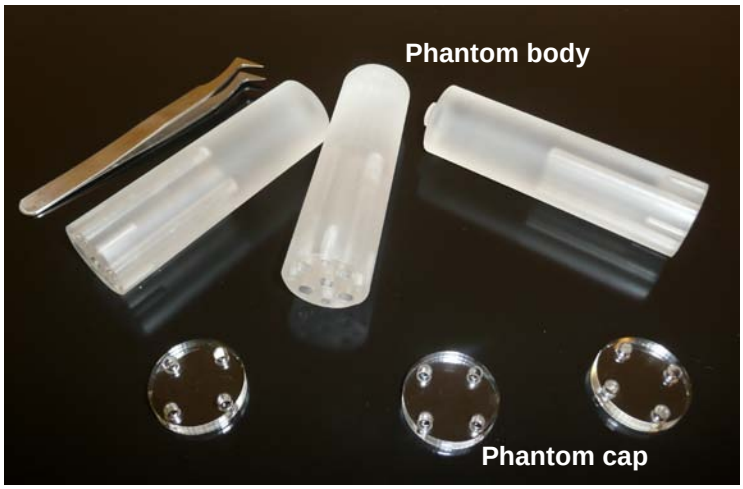

Figure 3. A picture showing the bodies and caps of the Aβ-phantom made of PMMA for the tasks to be carried in SA#2.

Table 1. Phantom configuration and Aβ-peptide concentration[10] (Unit of molar concentration: pm/g).

Phantoms	I	II	III	IV
Image quality	H_2O	POM: $(CH_2O)_n$	PTFE: $(C_2F_4)_n$	LDPE: $(C_2H_4)_n$
Aβ-Peptide (pmol/g)	APP (2/2)	$Aβ_{1-40}/Aβ_{1-42}$ (2/2)	$Aβ_{1-40}/Aβ_{1-42}$ (33/1117)	$Aβ_{1-40}/Aβ_{1-42}$ (661/2100)
Aβ-Peptide:Aβ-fibril (pmol/g)	APP (2/2)	$Aβ_{1-40}/Aβ_{1-42}$-Peptide: $Aβ_{1-40}/Aβ_{1-42}$-Fibril (0.5/0.5:0.3/1)	$Aβ_{1-40}/Aβ_{1-42}$-Peptide: $Aβ_{1-40}/Aβ_{1-42}$-Fibril (1.6/9:19/1172)	$Aβ_{1-40}/Aβ_{1-42}$-Peptide: $Aβ_{1-40}/Aβ_{1-42}$-Fibril (4.4/11.1:159/1659)

C. System integration: The prototype x-ray phase contrast CT is being constructed and optimized in the PI's laboratory. Shown in the picture presented in Fig. 4 are the major subsystems and components, including the micro-focus x-ray tube, CMOS x-ray detector at $48\mu m$ detector cell dimension, rotation stage, gratings G1 and G2 (Fig. 4 (a)), x-ray generator (Fig. 4 (b)), as well as the controlling system (Fig. 4 (c)) to coordinate and synchronize the phantom stage rotation, x-ray exposure and projection data acquisition, transferring and storage. All these components are integrated into the x-ray phase contrast CT system installed on the top of an optical table located in a room of the PI's laboratory with x-ray shielding.

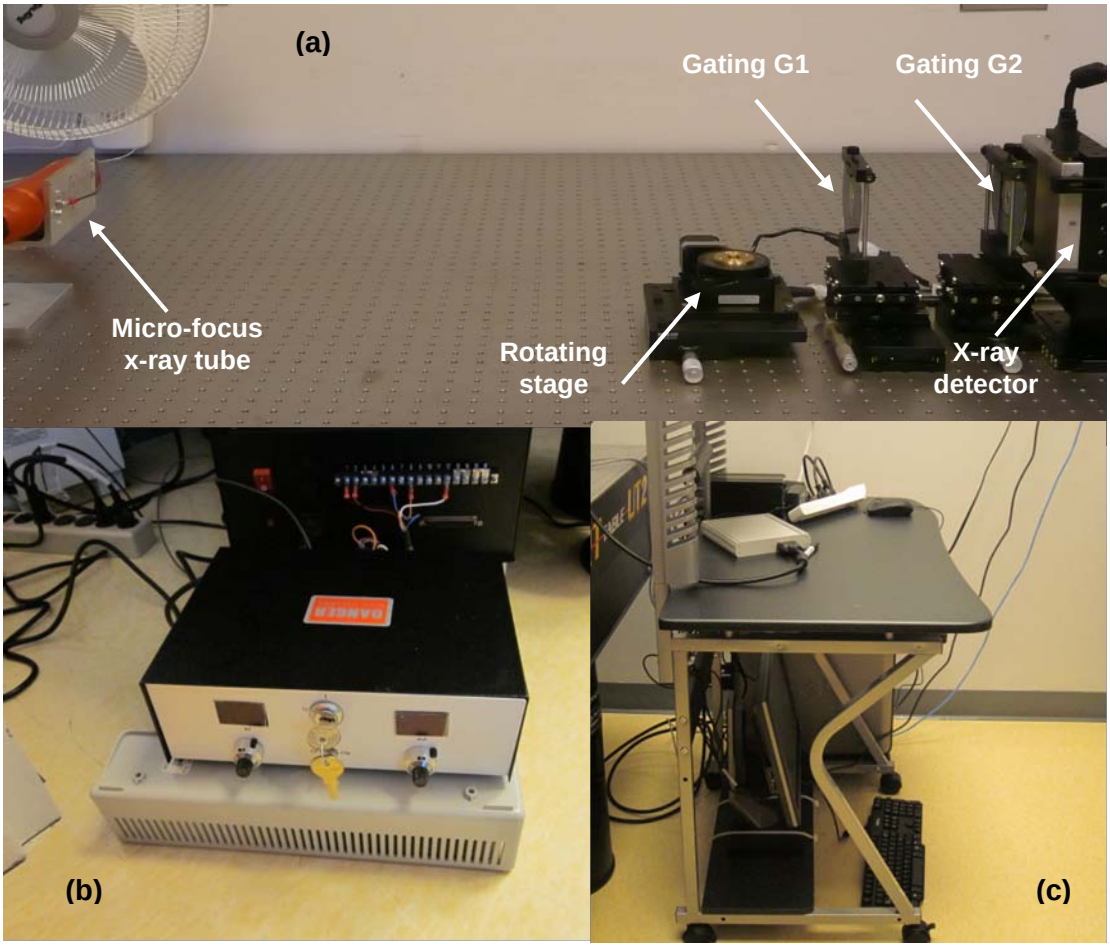

Figure 4. Pictures showing the prototype x-ray phase contrast CT: (a) deployment of x-ray tube, rotation stage, x-ray detector and gratings on the optical table, (b) x-ray generator and (c) system controller.

D. **System optimization**: One of the major challenges in x-ray CT system integration is that any imperfection in the x-ray detector's performance, even though its magnitude is only 0.1% relatively to what is supposed to be, may result in severe ring artifacts[11]. Illustrated in Fig. 5 (a) is an example of the images obtained using the attenuation-based counterpart of the prototype x-ray phase contrast CT system built in the PI's laboratory, wherein ring artifacts exist. The image reconstruction algorithm in reference[12] was utilized to reconstruct the CT images. As demonstrated in Fig. 5 (b), with a specially designed post-image-formation algorithm, the ring artifacts were removed completely. It is believed that, since this ring removal algorithm is post-image-formation, it will be able to remove the ring artifacts that will inevitably exist in the images generated by the x-ray phase contrast CT developed in this project.

In addition, we are in the process of developing the pre-reconstruction algorithms to remove the beam-hardening artifacts that can exist in the x-ray phase CT imaging. Both low frequency and high frequency components are being taken into account in the development.

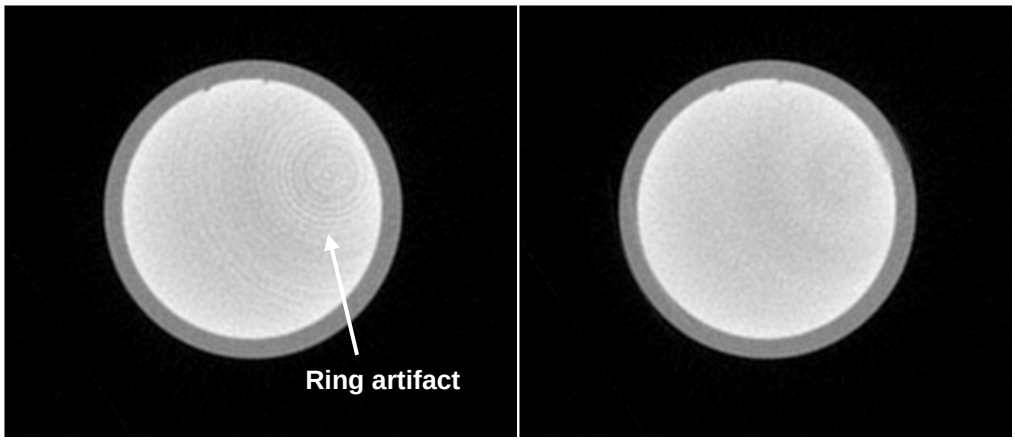

Figure 5. Images of a water phantom to show (a) the ring artifact caused by the imperfection in x-ray detector and (b) its removal with a specially designed post-reconstruction algorithm.

E. **Preliminary System performance**: In general, the imaging performance of a CT system is assessed by its low contrast detectability, spatial resolution and temporal resolution. As specified in the SOW, the goal of this research project is to develop the x-ray phase contrast CT imaging method for early detection of amyloid plaque in Alzheimer's disease. Because the amyloid plaques are small in size and low in contrast against the surrounding tissues, the x-ray phase contrast CT imaging of amyloid plaques requires superior spatial resolution and low contrast detectability simultaneously.

a. **Spatial Resolution**: As indicated and experimentally evaluated in reference[8,13], the spatial resolution of an x-ray phase CT is virtual identical to that of its attenuation-based counterpart, i.e., the conventional CT (namely virtual equivalence of spatial resolution). The figure of merit (FOM) to assess the spatial resolution of a conventional CT system is the MTF (modulation transfer function). The methods for gauging the MTF of a conventional CT system have been well established in the literature[14], in which a high contrast thin object, such as a thin metal wire, is usually employed. In principle, the wire should be thinner than the x-ray detector cell's dimension. However, the detector cell dimension of the prototype x-ray phase contrast CT in our investigation is $48\mu m$. Note that, a wire that is thinner than $48\mu m$ may not be able to withstand the force exerted on it to keep it straight and parallel to the CT's axis of rotation during the projection data acquisition process. Hence, alternatively, using a wire of approximately $100\mu m$ diameter, we measure the MTF of the CT system with two detector cells binned together and the result attained is presented in Fig. 6. In such a way, the MTF of the conventional counterpart of the x-ray phase contrast CT without the $2\times$ detector cell binning, i.e., at the default $48\mu m$ detector cell dimension, can be approximately obtained through proportional projection. Moreover, due to the virtual equivalence in the spatial resolution[8,13] between the x-ray phase contrast CT and the conventional CT, we can indirectly obtain the MTF of the x-ray phase contrast CT that is being built and optimized in this project.

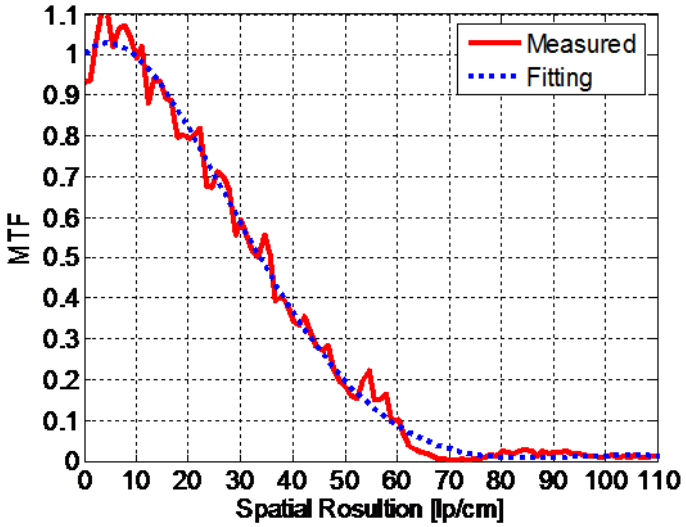

Figure 6. The MTF corresponding to the attenuation-based counterpart of the x-ray phase contrast CT with 2 detector cells binned together, which can be used to estimate the projected MTF corresponding to the x-ray phase CT without detector cell binning.

b. Low Contrast Detectability: The low contrast detectability of an x-ray phase contrast CT is substantially dependent on the opo-mechanical performance of grating G1 and G2. Hence, with further optimization on the opto-mechanical performance of G1 and G2 in progress, it would be premature to report the low contrast detectability of the prototype x-ray phase contrast CT at this moment. With a full access to the cutting-edge opto-mechanical and chemical equipment/devices at the GaTech's NTRC and its staff's very strong and knowledgeable support in recipe and process optimization, it is believed that the gratings G1 and G2 with relatively satisfactory opto-mechanical properties will eventually be obtained.

Key Research Accomplishments

- **System Construction:** A prototype x-ray phase contrast CT with its performance, especially the performance of its key components – G1 and G2, in the process of optimization.

- **Investigation of NEQ(k):** An observation made and reported by the PI's group first time in the literature[9] that the x-ray phase CT makes use of x-ray photons as efficiently as that of the conventional CT, although their noise power spectrum NPS(k) are dramatically different.

- **Investigation of 2nd Derivative**: An observation made and reported by the PI's group first time in the literature that the 2nd-order derivative, in addition to the 1st-order derivative, also plays a significant role in the x-ray tube and grating-based dark-field imaging[15].

Reportable Outcomes: So far, two papers related to the project have been published in Medical Physics, one of the leading scientific journals in medical Imaging. In addition, 5 papers have been published in international

conferences, such as the SPIE Medical Imaging Conference and IEEE Medical Imaging Conference. In addition, it is worthwhile mentioning that one team member (a post-doc fellow) who is partially supported by this award has been promoted to the position of research associate at Emory University School of Medicine.

A. Publication in Peer-reviewed Journals

1. Tang X, Yang Y and Tang S, "Characterization of imaging performance in differential phase contrast CT compared with the conventional CT – Spectrum of noise equivalent quanta NEQ(k)" *Med. Phys.,* 39(7): 4467-82, 2012.
2. Yang Y and Tang X, "The second-order differential phase contrast and its retrieval for imaging with x-ray Talbot interferometry," *Med. Phys., v.39,* pp.7237-53, 2012.

B. Publication in Peer-reviewed Conferences

1. X Tang, Y Yang and S Tang, "The potential imaging performance of differential phase contrast CT – NPS(k), MTF(k) and NEQ(k)," *Proc. 2nd International Conf. Image Formation in X-ray CT,* pp.271-74, 2012.
2. X. Tang, Y. Yang and S. Tang, "NEQ(k): The signal and noise transfer properties in differential phase contrast CT," 54th AAPM (American Association of Physicists in Medicine) annual Meeting, Charlotte, NC, July 29 – Aug. 2, 2012.
3. X. Tang, Y. Yang and S. Tang, "The property of signal-to-noise and its variation over spatial frequency in differential phase contrast CT," IEEE Medical Imaging Conference, Anaheim, Oct. 27 – Nov. 3, 2012.
4. X. Tang, Y. Yang and S. Tang, "Spectrum of noise equivalent quanta NEQ(k) – Differential phase contrast CT vs. conventional CT," RSNA 98th Scientific Assembly and Annual Meeting Program, Chicago, Nov. 25 – 30, 2012.
5. X Tang, Y Yang and S Tang, "Detectability index of differential phase contrast CT compared with conventional CT: a preliminary channelized Hotelling observer study," *Proc. SPIE,* v.8668, 2013.

Conclusion: As this is the annual report of the project's year 1, only discussions are given below:

- Overall, the project's progression is on track. The fabrication of the two key components – gratings G1 and G2 – is anticipated to be very challenging. It turns out, according to the experience in the first year, that to get the gratings G1 and G2 with adequate opto-mechanical properties is yet more challenging than anticipated.

- The PI has full access to the cutting-edge equipment/devices at GaTech's NTRC and fully supported by the GaTech NTRC's technological staff in the optimization of recipe and process. With more intensive effort devoted to speeding up the optimization, it is expected that the gratings G1 and G2 with satisfactory opto-mechanical properties will be obtained soon, such that the tasks towards SA#2 and SA#3 can be carried out on time.

- With the valued support by this award, the research group led by the principal investigator at Emory University has established an international scientific leadership in x-ray phase contrast CT imaging, demonstrated by its publication in the prestigious scientific journals and conferences, and the invitation by journal's editorial board to review manuscripts, and by federal and non-profit funding agencies for the study sections to review research proposals related to x-ray phase contrast CT imaging.

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